Chromosome 17 abnormalities in haematologic malignancies are important because the \( TP53 \) tumour suppressor gene is found on 17p 13.1. Chromosome 17 abnormalities were reported in 49 (4.3%) of cases in a study of patients with myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). In this cohort, 14 patients had monosomy 17 and 35 patients had unbalanced translocations between chromosome 17p and another chromosome. Most of them also had other cytogenetic abnormalities and 10 were therapy related, 69% also had a \( TP53 \) mutation. The pseudo Pelger-Huët like anomaly and vacuolated neutrophils were described in 70% of these patients. Chromosome 17 abnormalities have also been associated with therapy related myeloid neoplasms, unbalanced translocations involving chromosome 17, monosomy 17 and isochromosome 17q or 17p deletion having been reported. Isochromosome 17q occurs when chromosome 17 has two identical arms, i.e. no “p” arm but two “q” arms. This results in a cell having only one copy of 17p and three copies of 17q. It is thought to occur due to breakage of the proximal part of 17p followed by rejoining of the centromere containing chromatids and inactivation of one centromere. Isochromosome 17q has been reported in a variety of haematologic and solid malignancies, it is usually associated with a complex karyotype but has less commonly been reported in isolation. Myeloid neoplasms with isolated i(17q) have been reported to have features of an MDS/myeloproliferative neoplasm (MPN) overlap syndrome. Myeloid dysplasia, monocytosis and a high propensity for leukaemic transformation with a short overall survival are features of this condition.

Myeloid sarcoma (MS) is characterized by extramedullary tumour masses composed of myeloblasts or myelomonocytic cells. MS may present de novo or occur concomitantly with MDS, MPN or AML. Alternatively MS may represent transformation of a MPN or MDS to AML or occur at relapse. Fluorescence in situ hybridization analysis of 49 MS specimens showed clonal abnormalities in 25, specifically, monosomy 7 (10%), trisomy 8 (10%) and \( MLL \) gene rearrangement (8.5%). Concordance between fluorescence in situ hybridization on the MS specimen and bone marrow karyotyping was shown in 10 of 14 cases in which both analyses were performed. Interestingly, t(8;21) has been found in paediatric cases of MS and in orbital tumours. Comparative genomic hybridization (CGH) of seven MS cases showed chromosome 8 abnormalities in 3, with other abnormalities including loss of 4q, 6q, 12p and gain of 11q, 13q, 19 and 21. Li and co-workers performed next generation sequencing of 21 AML/MDS related genes in 6 cases of MS. They detected mutations in tyrosine kinases (\( FLT-3 \) and \( KIT \)), the \( WT1 \) tumour suppressor gene, the epigenetic regulators \( EZH2 \), \( ASXL1 \) and \( TET1 \) as well as \( SF3B1 \), an RNA splicesome protein. This study showed a genetic overlap between MS and AML, it is likely however that there are differences between these entities which account for the extramedullary localization of MS. A patient with AML and concomitant testicular MS was found to have i(17q) as part of a near tetraploid karyotype on cytogenetic analysis of the

**TO THE EDITOR**

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bone marrow. Genomic analysis of the MS tissue was not however performed in this case. It is noteworthy that i(17q) has not been reported previously in a tissue biopsy of MS.

A 79 year-old male presented with a one month history of lethargy and ankle oedema. He had no bleeding symptoms and denied weight loss, night sweats, fever or rash. Physical examination revealed bilateral cervical lymphadenopathy and moderate splenomegaly. Initial investigations revealed; haemoglobin 11.0 g/dL, white blood cells 17.8 x 10^9/L, neutrophils 7.3 x 10^9/L, monocytes 3.2 x 10^9/L, eosinophils 1.42 x 10^9/L, and basophils 1.96 x 10^9/L. A peripheral blood film showed dysplastic neutrophils and monocytes with platelet anisocytosis. A left shift was seen with blasts comprising 8% of white blood cells (Fig. 1a). His bone marrow aspirate and trephine were hypercellular with dysplastic granulopoiesis and megakaryopoiesis. Myeloblasts comprised 19% of nucleated cells with eosinophilia (12%) and basophilia (4%) (Fig. 1b & 1c). Multiparameter flow cytometry showed dyscoordinated granulocytic maturation with CD34 positive myeloblasts comprising 13% of events.

He underwent a cervical lymph node biopsy, which showed effacement of the lymph node architecture and infiltration with myeloblasts staining positive for CD34 and CD117 by immunohistochemistry, consistent with MS of the myeloblastic type (Fig. 1d & 1e). Flow cytometry of the lymph node confirmed the presence of CD117^+/HLA-DR^+ myeloblasts and HLA-DR^bright/CD117^dim monoblasts (Fig. 1f). Bone marrow karyotyping revealed a karyotype of 46, XY i(17)(q10)[12]/46,XY[8] (Fig. 2). Reverse transcriptase polymerase chain reaction for the FIP1L1-PDGFRα and BCR-ABL transcripts were negative, as was polymerase chain reaction for the JAK-2 V617F mutation. We performed array CGH (OncoscanTM) on the lymph node specimen which showed a gain of 17q and loss of 17p, consistent with i(17q), and no other significant copy number abnormalities (CNA) (Fig. 3). In summary, this patient had chronic myelomonocytic leukaemia 2 associated with i(17q), transforming to AML with a concomitant MS. In view of his age he was managed conservatively and eventually succumbed to the disease.

To the best of our knowledge, this is the first report of i(17q) being demonstrated in MS. The presence of i(17q) as the sole copy number abnormality in the MS specimen by CGH strongly suggests that i(17q) is contributing to the pathogenesis of MS. The molecular basis of i(17q)-mediated leukaemogenesis has not been well described. Sequencing of the TP53 gene in 17 patients with haematologic malignancies associated with i(17q) showed no TP53 mutations, suggesting the presence of an alternative tumour suppressor gene on chromosome 17. Transfection of a TP53 deficient cell line with an intact chromosome 17 from a TP53 mutant cell line lead to a reduced tumour growth. This provides functional evidence for the presence of an alternative tumour suppressor gene on chromosome 17p.

The heterozygous deletion of chromosome 11B3 has recently been shown in mice to be a potential driver of leukaemia and lymphoma in this context. Further studies are required for definitive identification of the gene(s) involved in humans.

An alternative explanation for i(17q) mediated neoplasia is the presence of oncogenes on 17q. Genes coding for signaling proteins of the N-Myc and c-Myc oncogene pathways (nm23-H1 and nm23-H2) are found on chromosome 17q. Neuroblastomas with an unfavourable prognosis commonly have Myc overexpression together with a gain of 17q which is hypothesized to play a role in the pathogenesis of these tumours.

The ERBB2 (HER2) oncogene is located on 17q, and the over expression of HER 2 has been implicated in solid malignancies as well as B-acute lymphoblastic leukaemia. The role of HER2 in myeloid malignancy is not certain but it is reasonable to speculate whether it could play a role in i(17q) related neoplasms. HER2 expression in i(17q) associated malignancies would be of clinical relevance given the availability of trastuzumab as a therapeutic option.

Tissue inhibitor of metalloproteinase 2 (TIMP-2) plays an important role in tissue homeostasis. TIMP-2 is overexpressed in the highly tissue invasive SH1 AML cell lines as well as bone marrow from AML patients. It was postulated that the overexpression of TIMP-2 could contribute to the tissue invasive properties of myeloblasts. The TIMP-2 gene is located on 17q and it maybe overexpressed in i(17q) related myeloid neoplasms. The tissue invasive properties conferred by TIMP-2 overexpression could provide a link between i(17q) and MS. The mechanism of i(17q) mediated neoplasia was not further investigated in our patient due to inadequate material. Further studies to explore these potential oncogenic pathways in MS are called for.

Myeloid malignancies associated with i(17q) have a dismal prognosis. In young patients, intensive chemotherapy followed by allogeneic stem cell transplant would be appropriate. Unfortunately, many of these patients are elderly and ineligible for intensive therapy. There is an urgent need for effective targeted therapy and future studies should focus on identifying actionable targets in this disease.

In conclusion, we present the first report of i(17q) demonstrated in a tissue biopsy of MS. Further studies using next generation sequencing are required to delineate the genetic architecture of MS with a view to development of novel therapeutic options.
Isochromosome 17q in myeloid sarcoma

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The authors declare that they have no conflict of interest.

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Fig. 1. Cytological, histological and flow cytometric findings of peripheral blood, bone marrow and lymph node. (1a) Peripheral blood film showing red cell anisocytosis, hypolobulated, dysplastic neutrophils and monocytes as well as platelet anisocytosis and hypogranularity. (1b) High power view of the bone marrow aspirate. Red arrows indicate hypolobulated, hypogranular myeloid precursors. Yellow arrows indicate large hypogranular platelets while the green arrow indicates a myeloblast. (1d & 1e) The lymph node is partially effaced by a monotonous population of blast cells with scanty cytoplasm. Immature eosinophilic precursors (arrows) are also present (1d, H&E, original magnification x 600). The blast cells are positive for CD117 (1e, CD117, original magnification x 600). (1f) Flow cytometry of the lymph node. The purple events are HLA-DR positive, CD117 heterogeneous monoblasts. The grey events are HLA-DR positive, CD117 positive myeloblasts. The yellow events are normal lymphocytes.
Fig. 2. Bone marrow karyotyping revealed a karyotype of 46,XY,i(17)(q10)[12]/46,XY[8].

Fig. 3. Array comparative genomic hybridisation. A mosaic gain of 17q and loss of 17p is demonstrated. This pattern is consistent with i(17q).
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